# PATENT SPECIFICATION 905,000

NO DRAWINGS.

*Date of Application and filing Complete Specification :*
*May 23, 1961.* *No. 18505/61.*

*Application made in United States of America (No. 33895) on June 6, 1960.*

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Index at Acceptance :—Class 81(1), B(3 : 4 : 6).

International Classification :—A61k.

## COMPLETE SPECIFICATION

# Improvements in and relating to Sustained and Delayed Release Oral Medicaments.

ERRATA

SPECIFICATION NO. 905,000

Page 2, line 20, *after* "aqueous" *insert* "acid".

Page 4, line 36, *for* "paseds" *read* "passed"

Page 4, line 37, *for* "125g" *read* "1.25g"

Page 4, line 39, *for* "intmo" *read* "into"

Page 4, line 41, *for* "usingm" *read* "using"

Page 4, line 98, *for* "claied" *read* "claimed"

PATENT OFFICE,
5th October, 1962

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release of the drug.

Early attempts to achieve delayed release of medication involved the formation of a coating over a core of the active drum using an acid-resistant substance such as shellac. The difficulty with this type of oral medication was that if the coating was too thin it broke down in the stomach, releasing the medication too soon and if it was too thick the tablet was excreted practically intact. Furthermore, as is the case with all enteric-coated tablets, even if the coating is carefully adjusted to dissolve or break down in the bowel, all of the drug is immediately released, resulting in a peak action with no further action thereafter. A typical enteric coating material is shellac and a further diffi-

ionic exchange with the digestive juices ... the intestinal tract. These procedures are quite costly because of the amount of labor involved in preparing the compositions and because of the cost of the special resins. Moreover, in the case of the ion exchange resins, a sustained release effect is not always obtained.

In accordance with the invention, a solid medicinal component is mixed with a special polymeric material that is substantially insoluble in water. The polymeric material used is the acid form of a polymer prepared as described in United States Patent No. 2,798,053, granted July 2, 1957, selectively utilizing from 1% to 2% by weight of polyalkenyl polyether, for example, polyallyl

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## Improvements in and relating to Sustained and Delayed Release Oral Medicaments.

We, AMERICAN HOME PRODUCTS CORPORATION, a Corporation organized and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 17, State of New York, United States of America (Assignee of DAVID MAYRON), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to therapeutic compositions with delayed release action including the ability to release medication gradually over a relatively long period of time, and methods for preparing them.

Various procedures have been proposed for delaying or prolonging the release of medicaments in oral form but such proposals have not resulted in completely satisfactory products either from the standpoint of simplicity of manufacture or actual ability to achieve the desired smoothly sustained release of the drug.

Early attempts to achieve delayed release of medication involved the formation of a coating over a core of the active drum using an acid-resistant substance such as shellac. The difficulty with this type of oral medication was that if the coating was too thin it broke down in the stomach, releasing the medication too soon and if it was too thick the tablet was excreted practically intact. Furthermore, as is the case with all enteric-coated tablets, even if the coating is carefully adjusted to dissolve or break down in the bowel, all of the drug is immediately released, resulting in a peak action with no further action thereafter. A typical enteric coating material is shellac and a further difficulty develops when this material is used. When a freshly produced tablet having a shellac coating is prepared, its ability to resist stomach acids is satisfactory but this characteristic changes if the tablet is held on the shelf for a considerable period of time before use. In time the coating hardens to such an extent as to prevent even partial absorption of the drug in the intestinal tract, the tablet thus passing through the body substantially intact.

Where it is desirable to avoid sudden full action of the drug or the equivalent thereof, the art has developed procedures involving coating drug granules with varying thicknesses of hydrophobic or non-polar material and commingled granules of different coating thicknesses so that the thinly coated particles release drug earlier than the heavier coated particles. Other procedures involve the use of resins which either seek to achieve a slow leaching action or by the use of an ion-exchange resin, chemically bind or complex with the drug and then release it by an ionic exchange with the digestive juices of the intestinal tract. These procedures are quite costly because of the amount of labor involved in preparing the compositions and because of the cost of the special resins. Moreover, in the case of the ion exchange resins, a sustained release effect is not always obtained.

In accordance with the invention, a solid medicinal component is mixed with a special polymeric material that is substantially insoluble in water. The polymeric material used is the acid form of a polymer prepared as described in United States Patent No. 2,798,053, granted July 2, 1957, selectively utilizing from 1% to 2% by weight of polyalkenyl polyether, for example, polyallyl

sucrose as the crosslinking material, the remainder being essentially an olefinically-unsaturated carboxylic acid monomer containing at least one carbon-to-carbon olefinic double bond and at least one carboxyl group such as acrylic acid and the polymerization being carried out in a hydrocarbon diluent with a free radical catalyst, for example, benzoyl peroxide. The polymer particularly preferred may be identified as "Carbopol 934" under which Registered Trade Mark this acid polymer is sold by B. F. Goodrich Chemical Company.

The term solid medicational component as used herein means solid drugs or drugs mixed with conventional carriers or diluents. Desirably, an agent capable of preventing the rapid release of a drug should be one which does not readily hydrate or dissolve in an aqueous environment as is found in stomach juices. To achieve sustained and uniform release of drug it is desirable that the agent should hydrate or slowly dissolve in the intestinal tract and therefore in that environment where wildly alakaline conditions may be found. It has been discovered that the acid form of the aforesaid carboxy vinyl polymers coming first in contact with the aqueous acid contents of the stomach does not dissolve or hydrate to any appreciable extent but when it enters the alkaline area of the intestinal tract, the polymer is neutralized, hydrates and becomes water soluble. Actually as a result of the neutralization a gel sheath froms around the tablet which has the effect of reducing the rate or release of the drug.

It may be seen that a water-soluble polymer would be quite ineffective for the purpose desired, namely, to produce a sustained release oral medication. Water solubility of the carrier agent would permit rapid disintegration of the tablet in the stomach with very early release of substantially all of the medication. This is contrary to the desired action which contemplates not more than a small amount of medication being released in the stomach with the greater amount being released in the intestinal tract.

When the substantially water-insoluble carboxy vinyl polymer as describe above is intimately mixed with ingredients care should be taken that the latter neither decompose, disintegrate nor chemically combine with the polymer. This can be specifically avoided by dry mixing the ingredients and, where chemical reaction is possible, by using relatively neutral salts of the desired medicinal.

The drug that is to be associated with the carboxy vinyl polymer may be any medicament where a delayed or sustained release effect is desired and which fufills the criteria mentioned previously. It should preferably be an acid or a salt which does not change the *p*H of material portions of the carboxy polymer or of the tablet itself. This means that if a drug to be utilized in the composition is basic in reaction, it should be used as a salt, and preferably as a neutral salt as mentioned previously. This would exclude strongly alkaline salts such as alkali metal and alkaline earth metal carbonates or bicarbonates but would permit the use of relatively mild basis compounds, for example sympathomimetic amines or phenothiazine compounds, preferably as salts. Among the medicinals contemplated as being usefully employed for sustained release may be mentioned analgesics, antispasmodics, hypotensive agents, sympathomimetics, muscle relaxants, ataractics, antibiotics, anticonvulsants, antihistamines, coronary and peripheral vasodilators, fungistatic agents, antinauseants, central stimulants, parasympathetic inhibitors, and antipruritics, to name the most obvious and important therapeutic classes where a prolonged or delayed release action is desirable.

The compositions of the invention are utilized in the form of tablets which are prepared either in the form of coated or uncoated tablets, preferably the latter.

The preferred form of sustained release tablets is prepared by first intimately mixing the selected drug and carboxy vinyl polymer in the dry state. Sufficient polymer is used to provide for a sustained release of the drug overa period of at least 5 hours and preferably over a period of about 12 to 14 hours. In general, when a relatively water-insoluble drug is used or when the drug dosage is in the neighbourhood of about 200 mg, the ratio of polymer to drug should be about 1:1 on a weight basis. Where large amounts of drug are required, substantially above 200 mg, for example, a ratio of less than 1:1 is utilized, to as low as about 0.5:1, polymer to drug On the other hand, if the drug is relatively water soluble or if the dosage contemplated is below about 10 mg, the ratio of polymer to drug would be substantially greater than 1:1, for example, going as high as about 100:1. In any case, the total weight of the tablet should not be substantially greater than about 1,000 mg. It will be understood therefore that even with large amounts of a drug, one obtains the desired sustained release effect of the polymemr with as little as about 0.5:1, polymer to drug. Within the limits given the ratio of polymer to drug may be changed somewhat to produce a change in the rate of release where this is desired.

In the preparation of uncoated tablets the contemplated drug in the desired dosage amount is intimately mixed with the carboxy vinyl polymer and tabletting lubricant, as for example magnesium stearate, talc or like material. Well known excipients and/or

binders may also be added if desired. The mixture is then compressed into finished tablets, or if a high degree of uniformity is desired, the mixture is compressed into large, unfinished shapes known as "slugs". The latter are then crushed and the particles are forced through a sieve of about No. 10 to 30 U.S. standard size.

The particles of intimately mixed drug or drugs and carboxy vinyl polymer produced by the crushing operation are now mixed with additional lubricant and the dry mix is tableted in a typical tabletting machine to form tablets containing a very small amount of the drug or drugs on the surface with the remainder intimately and uniformly dispersed throughout the tablet.

When it is desired to start the uniform release of drug only after the tablet composition has entered the intestinal tract, the uncoated tablet as produced above may be coated with acid carboxy vinyl polymer by itself. Thus, the sieved particles obtained as previously described are formed into a core by a tablet-forming machine and a coating is prepared by mixing carboxy vinyl polymer with about 0.5% by weight of lubricant. The coating mixture is slugged, granulated and passed through a sieve of the size indicated above. More lubricant (about 0.5%) is added and using a machine that applies a coating onto a core, the coating mixture is applied to the core as previously prepared.

When only an enteric coated tablet is desired which has good shelf life and which will provide a substantial drug action only after the medication has entered the intestinal tract; the selected drug is combined with one or more conventional excipients such as lactose or calcium carbonate. This mixture is then granulated and forced through a sieve of a size within the range previously indicated. The particles are combined with a lubricant, for example talc or magnesium stearate. The mixture is then compressed to form a tablet core which is then coated with a carboxy vinyl polymer coating in the manner previously described.

The following examples further illustrate the invention previously described.

EXAMPLE 1.

50 g of mephentermine sulphate powder are mixed with 445 g of Carbopol 934 powder and 2.5 g of magnesium stearate. The powder mixture is compressed into tablets which are then crushed and the particles forced through a No. 20 U.S. standard sieve. To the granules thus obtained are added 2.5 g of magnesium stearate and the mixture is then compresesd into tablets weighing approximately 500 mg with a diameter of about ½ inch in size. When tested on a Strong-Cobb hardness tester, the tablets had a hardnes of 22 kg.

EXAMPLE 2.

Sustained release mephentermine tablets were prepared by the procedure described in Example 1 but varying the polymers and the amounts per tablet. The ingredients per tablet were as follows:—

| | |
|---|---|
| Mephentermine sulphate powder | 5.00 mg |
| Carbopol 940 ... ... ... ... | 44.50 mg |
| Mg stearate ... ... ... ... ... | 0.50 mg |

EXAMPLE 3.

Sustained release promabine tablets were prepared by the procedure described in Example 1 utilizing the following ingredients and amounts per tablet:—

| | |
|---|---|
| Promazine hydrochloride powder | 100 mg |
| Carbopol 934 powder ... ... ... | 395 mg |
| Magnesium stearate USP ... ... | 5 mg |

EXAMPLE 4.

Sustained release promazine tablets pared by the procedure disclosed in Example 1 utilizing the following ingredients and amounts per tablet:—

| | |
|---|---|
| Crystalline acetylsalicyclic acid (40 mesh USP) ... ... ... | 324 mg |
| Carbopol 934 powder ... ... | 129.6 mg |
| Magnesium stearate USP ... ... | 3.2 mg |

The tablets so prepared had a diameter of approximately $^{7}/_{16}$ inch and a hardness of 25 kg.

EXAMPLE 5.

Sustained release penicillin tablets were prepared by the procedure disclosed in Example 1 utilizing the following ingredients and amounts per tablet:—

| | |
|---|---|
| Potassium phenoxymethyl penicillin | 275 mg (420,000 units) |
| Carbopol 934 powder ... ... | 245 mg |
| Magnesium stearate USP ... ... | 7.5 mg |

EXAMPLE 6.

Prolonged release analgesic tablets containing ergotamine were prepared in accordance with the procedure of Example 1 producing analgesic tablets containing 3 mg of ergotamine tartrate, 347 mg of Carbopol 934 powder, and 5 mg of magnesium stearate USP per tablet.

EXAMPLE 7.

To prepare an enteric-coated analgesic medication, a core granulation was made up with the following ingredients and amounts:

| | |
|---|---|
| Sodium salicylate USP ... ... ... | 325 g |
| Lactose USP ... ... ... ... ... | 65 g |
| Gelatine USP ... ... ... ... ... | qs |
| Starch USP ... ... ... ... ... | 15.6 g |
| Talc USP ... ... ... ... ... | 15.6 g |

A wet granulation was prepared from the sodium salicylate and lactose with the gelatin solution. The wet granulation was forced through a No. 14 U.S. standard sieve and the granules were allowed to dry. The dried granules were then mixed with the starch and talc and this mixture was then compressed to form the core of the tablets.

A coating formulation was made up using 100 g of Carbopol 934 powder and 0.5 g of magnesium stearate USP. The mixture was compressed into slugs which were then granulated and passed through a No. 20 U.S. standard sieve. To the granules as formed was added 0.5 part by weight of magnesium stearate and, using a machine that applies a coating onto a core, the coating granulation was compressed as a coating on the original core preparation. By using a flat beveled punch of $^{11}/_{32}$ inch size a core for a tablet weighing approximately 388 mg was obtained and by using a flat beveled punch of $^{7}/_{16}$ inch size a coating for the tablet weighing 280 mg was obtained.

EXAMPLE 8.

A combined sustained release and enteric-coated tablet was prepared by first forming sustained release cores containing both medication and carboxy vinyl polymer and coating it with the latter. The material for the core was aminophylline utilizing 150 grams which was intimately mixed with 75 grams of Carbopol 934 and 1.25 g of magnesium stearate The powder mixture was formed into tablets or slugs, then crushed and paseds through a No. 20 sieve The granules were mixed with 125 g of magnesium stearate and were compressed and formed intmo cores weighing approximately 380 mg containing about 250 mg of aminophylline usingm an elongated, capsule-shaped punch. A coating of "Carbopol 934" (a Registered Trade Mark) was compressed onto the cores in the manner previously described to give a coating of 240 mg per core.

WHAT WE CLAIM IS:—

1. A delayed release pharmaceutical preparation in oral dosage form which is a tablet comprising a solid medicinal component and a water insoluble, acid carboxy vinyl polymer in the form of a copolymer of an olefinically unsaturated carboxylic acid monomer containing at least one carbon-to-carbon olefinic double bond and at least one carboxyl group combined with from 1 to 2% by weight of a polyalkenyl polyether as a cross-linking agent.

2. A preparation as claimed in Claim 1, in which the tablet comprises an intimate mixture of the solid medicinal component and the water insoluble, acid carboxy vinyl polymer.

3. A preparation as claimed in Claim 2, in which the tablet is also covered with a coating of the water insoluble, acid carboxy vinyl polymer.

4. A preparation as claimed in Claim 1, in which the tablet comprises a core comprising the solid medicinal component covered with a coating of the water insoluble acid carboxy vinyl polymer.

5. A delayed release pharmaceutical preparation in tablet form as hereinbefore described with reference to and as illustrated in any of the examples.

6. A process for the production of the delayed release pharmaceutical preparation in oral dosage form as claimed in any of the preceding claims which comprises intimately mixing the comminuted solid medicinal component with the water insoluble, acid carboxy vinyl polymer and compressing the mixture to form the tablet.

7. A process as claimed in Claim 6, in which the intimate mixture of comminuted solid medicinal component and polymer are fomed into slugs which are crushed and screened, the particles being mixed with a tabletting lubricant and the mixture compressed into tablets.

8. A process as claimed in Claim 6 or 7 in which the tablet is coated with additional acid carboxy vinyl polymer.

9. A process for the production of the delayed release pharmaceutical tablet as claied in any of Claims 1 to 5 which comprises compressing the comminuted solid medicinal component to form a core and coating the core with the water insoluble acid carboxy vinyl polymer.

10. A process for the production of the delayed release pharmaceutical tablet form as claimed in any of Claims 1 to 5 substantially as hereinbefore described with reference to and as illustrated in any of the examples.

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